- *Obstructive uropathy due to bladder outlet obstruction, a calculus, or other cause*
- *Vesicourethral reflux or other urologic abnormalities, including surgically created ileal loops*
- *Renal transplantation*

3. Clinically Evaluable Patients: All eligible patients that had:
   - received at least 5 days of treatment (at least 3 days for failures)
   - a pre-treatment culture positive ($\geq 10^5$ cfu/mL) for an uropathogen that was susceptible to both study drugs, *and*
   - not received any other presumably effective antimcrobial agent between the pre-treatment and the Test of Cure visit

4. Microbiologically Evaluable Patients: All clinically evaluable patients who had a quantitative urine culture performed at the Test of Cure visit.

Safety assessment included evaluation for adverse events up to two weeks after therapy with the study drug had terminated.

8.6.1.1.5 Termination and Clinical Follow-up

The protocol stipulated that patients would be discontinued for any of the following reasons: patient's request, patient noncompliance with protocol, intercurrent illness which would significantly affect clinical assessment, or require discontinuation (opportunistic infection was given as an example). The applicant also reserved the right to terminate the study at their discretion.

Clinical evaluations were to occur while on study drug therapy visit (Day 3), and post-therapy visit (Day 5 to Day 42 after termination of therapy). An extended follow-up visit was to occur between Day 29 and Day 42 post-therapy, if clinically indicated. The protocol stipulated that abnormal laboratory results were to be repeated until they returned to normal, or until they were deemed by the investigator to be unrelated to study drug treatment.

8.6.1.1.6 Sample Size and Statistical Plan

The study was designed on the premise that gatifloxacin's eradication rate would be similar to ciprofloxacin (65%) in treating complicated UTI. The applicant calculated that 120 evaluable patients per treatment arm would have 90% power to make the claim the lower bound of the 95% confidence interval for the difference in the eradication rates (gatifloxacin – ciprofloxacin) was greater than or equal to (–) 20%, with a two-sided $\alpha$-value of 0.05.

Sample size calculations were based on an assumed evaluability rate of 90%, therefore target enrollment was originally 134/arm (268 total). The target enrollment was revised 350 patients, when efficacy data became available from half of the patients. The projected evaluability rate was recalculated as 49%, and a pooled analysis of the two arms showed an eradication rate of 81%.

*Reviewer's Comments*

*The change in sample size calculations were submitted to the protocol in an amendment on 4 February 1998, specifically citing that the "microbiological cure" rate was going to be used for sample size calculations, rather than "clinical cure" rates.*

8.6.1.1.7 Study Results

8.6.1.1.7.1 Enrollment and Description of Patients Enrolled in the Study

During the time period from 20 August 1997 to 11 July 1998, 376 patients were randomized, and 372 patients took at least one dose of study drug. The following table, reproduced from the applicant's study report (Table 8.1A, p. 65), indicates the patient enrollment by site, as well as the number that were clinically and microbiologically evaluable.

**Patient Enrollment, by Investigator (Study AI420-031)**

| | | Number (%) of Patients | | | |
|---|---|---|---|---|---|
| Site | Investigator | Number Randomized | Number Treated | Number Clinically Eligible | Microbiologically Evaluable |
| 016 | B. Wachs, M.D. | 46 (100) | 45 (98) | 45 (98) | 11 (24) |
| 035 | T. Marbury, M.D. | 45 (100) | 45 (100) | 45 (100) | 32 (71) |
| 030 | K. Tomera, M.D. | 43 (100) | 43 (100) | 41 (95) | 14 (33) |
| 003 | S. Auerbach, M.D. | 20 (100) | 20 (100) | 19 (95) | 10 (50) |
| 004 | G. Brown, M.D. | 20 (100) | 20 (100) | 19 (95) | 13 (65) |
| 017 | R. Garcia, M.D. | 19 (100) | 19 (100) | 19 (100) | 7 (37) |
| 015 | W. Pittman, M.D. | 16 (100) | 16 (100) | 16 (100) | 14 (88) |
| 007 | F. Maggiacomo, D.O. | 15 (100) | 15 (100) | 15 (100) | 8 (58) |
| 026 | S. Freedman, M.D. | 15 (100) | 15 (100) | 14 (93) | 9 (60) |
| 023 | R. Sharifi, M.D. | 13 (100) | 13 (100) | 11 (85) | 4 (31) |
| 012 | J. Jensen, M.D. | 12 (100) | 11 (92) | 11 (92) | 5 (42) |
| 006 | E. Killorin, M.D. | 11 (100) | 11 (100) | 11 (100) | 3 (27) |
| 009 | S. Sarshik, M.D. | 11 (100) | 11 (100) | 11 (100) | 7 (64) |
| 010 | C. Cox, M.D. | 10 (100) | 10 (100) | 10 (100) | 10 (100) |
| 024 | G. Malek, M.D. | 10 (100) | 10 (100) | 10 (100) | 7 (70) |
| 008 | M. McFadden, M.D. | 9 (100) | 9 (100) | 9 (100) | 7 (78) |
| 029 | D. Gleason, M.D. | 9 (100) | 9 (100) | 9 (100) | 2 (22) |

| | | Number (%) of Patients | | | |
|---|---|---|---|---|---|
| Site | Investigator | Number Randomized | Number Treated | Number Clinically Eligible | Microbiologically Evaluable |
| 041 | P. McElvaine, M.D. | 7 (100) | 7 (100) | 1 (14) | 0 |
| 005 | R. Castellano, M.D. | 5 (100) | 5 (100) | 5 (100) | 3 (60) |
| 011 | H. Epstein, M.D. | 5 (100) | 4 (80) | 4 (80) | 1 (20) |
| 027 | R. Bettis, M.D. | 5 (100) | 5 (100) | 5 (100) | 3 (60) |
| 014 | M. Picone, M.D. | 4 (100) | 4 (100) | 4 (100) | 3 (75) |
| 046 | W. King, M.D. | 4 (100) | 4 (100) | 4 (100) | 3 (75) |
| 018 | C. Renneker, Jr, M.D. | 3 (100) | 3 (100) | 3 (100) | 3 (100) |
| 028 | L. Galdieri, M.D. | 3 (100) | 3 (100) | 3 (100) | 0 |
| 037 | E. Sōlomon, M.D. | 3 (100) | 3 (100) | 3 (100) | 3 (100) |
| 043 | L. Harbach, M.D. | 3 (100) | 3 (100) | 3 (100) | 1 (33) |
| 032 | W. L. Weems, M.D. | 2 (100) | 2 (100) | 2 (100) | 1 (50) |
| 034 | B. Kerzner, M.D. | 2 (100) | 2 (100) | 2 (100) | 1 (50) |
| 047 | G. Fadda, M.D. | 2 (100) | 2 (100) | 2 (100) | 0 |
| 031 | W. Moseley, M.D. | 1 (100) | 1 (100) | 1 (100) | 1 (100) |
| 036 | T. Parkey, M.D. | 1 (100) | 1 (100) | 1 (100) | 0 |
| 042 | H. Farris, M.D. | 1 (100) | 1 (100) | 1 (100) | 0 |
| 045 | W. Kessler, M.D. | 1 (100) | 0 | 0 | 0 |
| Total | | 376 (100) | 372 (99) | 356 (95) | 186 (49) |

*Reviewer's Comment*

*Of the four patients that did not receive any study drug, three had been assigned to ciprofloxacin:*

*Patient #011-0160 was a 70 year-old white male who actually did participate in the study, because he was reassigned to a different number (011-00163). The blister pack that was originally assigned to him did not contain any medications.*

*Patient #012-0022 was a 31 year-old white female who decided against participating in the study after she had signed the informed consent form. She did not want to risk acquiring a yeast infection.*

*Patient #016-0070 was a white male who initially agreed to participate in the study. The patient's information was relayed to the sponsor, who assigned*

*him a study number. The patient refused to enter the study after he read the informed consent form.*

*Patient #045-00446, was a 60 year-old male who was supposed to have received gatifloxacin. He did not receive study drug because after randomization, but before the study drug was dispense, it was identified that he had received systemic antibiotic therapy.*

The following table, adapted from the applicant's Study Report (Table 8.3, p. 70), and the Integrated Summary and Safety Report (Table 7.2, p. 332), summarizes the demographic characteristics of the patient population:

**Demographic Characteristics, All treated Patients (Study AI420-031)**

| Characteristic | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 189 | Ciprofloxacin N = 183 | Total N = 372 |
| Gender | | | |
| Female (%) | 105 (56) | 106 (58) | 211 (57) |
| Male (%) | 84 (44) | 77 (42) | 161 (43) |
| Race | | | |
| White (%) | 146 (77) | 139 (76) | 285 (77) |
| Black (%) | 21 (11) | 22 (12) | 43 (12) |
| Hispanic (%) | 15 (8) | 18 (10) | 33 (9) |
| Asian (%) | 6 (3) | 4 (2) | 10 (3) |
| Other (%) | 1 (<1) | 0 | 1 (<1) |
| Age (years) | | | |
| Mean | 54 | 54 | 54 |
| Median | 55 | 58 | 56 |
| Range | 19 - 94 | 18 - 93 | 18 – 94 |
| < 65 | 115 (61) | 108 (59) | 223 (60) |
| 65 – 74 | 30 (16) | 34 (19) | 64 (17) |
| ≥ 75 | 44 (23) | 41 (22) | 85 (23) |

*Reviewer's Comment*

*Overall, there were more females enrolled than males, and the predominant ethnic group was white. However, the distribution was similar between the two*

*treatment groups. In addition, the distribution was also comparable between the two groups with respect to ethnic group and age.*

8.6.1.1.7.2 Patient Diagnoses and Complicating Factors at Entry

The types of diagnoses and duration of infection are summarized in the following table, which is adapted from the applicant's Study Report (Table 8.4C, p. 73).

**Disease Diagnoses, All Treated Patients (Study AI420-031)**

| | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 189 | Ciprofloxacin N = 183 | Total N = 372 |
| Diagnosis | | | |
| Complicated UTI (%) | 146 (77) | 142 (78) | 288 (77) |
| Pyelonephritis (%) | 43 (23) | 41 (22) | 84 (23) |
| Duration of Infection (days)[a] | | | |
| Mean | 8.6 | 6.4 | 7.5 |
| Median | 5 | 4 | 4 |
| Minimum/Maximum | 1 – 120 | 1 – 90 | 1 - 120 |

[a] Three patients in the gatifloxacin group and one in the ciprofloxacin group had no recorded duration of infection.

*Reviewer's Comment*

*The distributions of diagnoses and duration of infection were comparable between the two treatment groups. It is noted that the sponsor was successful in enrolling sufficient number of patients with the diagnosis of pyelonephritis to allow inclusion of this diagnosis as one of the indications.*

The applicant evaluated the types, and number, of complicating factors that were present upon entry. These data are summarized in the following table, adapted from Table 8.4D in the applicant's Study Report, (p. 75).

**Complicating Factors at Study Entry, All Treated Patients (Study AI420-031)**

| | Number (%) of Patients* (%) | | |
|---|---|---|---|
| | Gatifloxacin N = 146 | Ciprofloxacin N = 142 | Total N = 288 |
| **No Complicating Factor** | **5 (3)** | **4 (3)** | **9 (3)** |
| **One Complicating Factor** | **98 (67)** | **84 (59)** | **182 (63)** |
| Impaired Bladder Emptying | 58 (40) | 53 (37) | 111 (39) |

| | Number (%) of Patients* (%) | | |
|---|---|---|---|
| | Gatifloxacin N = 146 | Ciprofloxacin N = 142 | Total N = 288 |
| Vesicoureteral Reflux (VUR) or Other Urologic Abnormalities (OUA)[a] | 12 (8) | 16 (11) | 28 (10) |
| Obstructive Uropathy | 17 (12) | 9 (6) | 26 (9) |
| Indwelling/Intermittent Catheter | 8 (5) | 3 (2) | 11 (4) |
| Ileal Loops | 2 (1) | 3 (2) | 5 (2) |
| Transplant | 1 (1) | 0 | 1 (<1) |
| **More Than One Complicating Factor** | **43 (29)** | **54 (38)** | **97 (34)** |
| Indwelling/Intermittent Catheter **plus**: | 32 (22) | 39 (29) | 71 (25) |
| Impaired Bladder Emptying | 26 (18) | 30 (21) | 56 (19) |
| VUR or OUA | 6 (4) | 4 (3) | 10 (3) |
| Impaired Bladder Emptying **plus** VUR or OUA | 0 | 3 (2) | 3 (1) |
| Impaired Bladder Emptying **plus** Obstructive Uropathy | 0 | 1 (1) | 1 (<1) |
| Obstructive Uropathy **plus** VUR or OUA | 0 | 1 (1) | 1 (<1) |
| Ileal Loops **plus**: | 2 (1) | 1 (1) | 3 (1) |
| VUR or OUA | 1 (1) | 1 (1) | 2 (1) |
| Indwelling/Intermittent Catheter **plus** VUR or OUA | 1 (1) | 0 | 1 (<1) |
| Impaired Bladder Emptying **plus**: | 8 (5) | 11 (8) | 19 (7) |
| VUR or OUA | 4 (3) | 6 (4) | 10 (3) |
| Obstructive Uropathy | 4 (3) | 5 (4) | 9 (3) |
| Obstructive Uropathy **plus** VUR or OUA | 1 (1) | 3 (2) | 4 (1) |

[a] This category does not include Ileal Loops.
* Pyelonephritis patients are excluded from this table.

*Reviewer's Comments*

*Although there are examples of numerical differences in one arm vs. another in several categories, it was not consistently in one treatment group. For example, there were more patients in the gatifloxacin treatment group with obstructive uropathy, but there were more patients in the gatifloxacin treatment group with vesicoureteral reflux. Clinical meaningful differences between the treatment groups did not occur, therefore, the overall impression is that the two treatment groups were comparable with respect to the number of complicating factors that were present at entry.*

8.6.1.1.7.3 Patient Disposition

Fifty-three patients (30 gatifloxacin patients and 23 ciprofloxacin patients) discontinued therapy prior to the completion of therapy. The largest category was "adverse event" – 22 patients, but this was comparable between the two treatment groups. The one category that appeared to have an imbalance was "Pathogen resistant to therapy." These data are summarized in the following table, which is adapted from the applicant's Study Report (Table 9.2, p.84):

**Reason for Discontinuation of Study Medication (Study A1420-031)**

| | Number (%) of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 189 | Ciprofloxacin N = 183 | Total N = 372 |
| **Discontinued Therapy Early** | 30 (16) | 23 (13) | 53 (14) |
| Adverse Event | 12 (6) | 10 (5) | 22 (6) |
| Pathogen Resistant to Therapy | 8 (4) | 1 (<1) | 9 (2) |
| Lost to Follow-Up | 3 (2) | 4 (2) | 7 (2) |
| Laboratory Abnormality | 1 (<1) | 1 (<1) | 2 (<1) |
| Patient Request | 1 (<1) | 2 (1) | 3 (<1) |
| No Pathogen Isolated | 0 | 1 (<1) | 1 (<1) |
| Other Antibiotic Given Before TOC Visit | 1 (<1) | 0 | 1 (<1) |
| Protocol Violation | 1 (<1) | 0 | 1 (<1) |
| Intercurrent Illness | 0 | 1 (<1) | 1 (<1) |
| Noncompliance | 3 (2) | 3 (2) | 6 (2) |

*Reviewer's Comments*

*As noted above, "resistant pathogen" was the only category where there seemed to be a significant imbalance between treatment groups. Four of the nine patients (=016-0068, =016-0142, #016-0198, and #016-0202) were from one center, which also was the site with the greatest enrollment. Review of the case report forms and microbiological data did not reveal any obvious connection between the patients. There was no apparent correlation with respect to their demographic data, or temporal association in their study enrollment. The resistant pathogens were E. coli, P. aeruginosa, and K. pneumoniae, and they manifested resistance to both study drugs. These findings were mirrored by the remaining five patients that had resistant pathogens.*

*With respect to discontinuation due to adverse events, there were similar incidence rates between the two treatment groups. Although there was a predominance of females in the gatifloxacin who were discontinued due to*

*adverse events (10 females vs. 2 males), this was mirrored in the ciprofloxacin treatment group (7 females vs. 3 males). There was no propensity within a treatment group with respect to age or ethnic group.*

*The most common adverse events that resulted in discontinuation of gatifloxacin were gastrointestinally related: nausea, vomiting, and/or diarrhea. Most were considered mild in severity, and causality ranged from "possible" to "certain."*

*Loss to follow-up was comparable between the two treatment groups. Review of the case report forms did not reveal any information that would raise concern that the loss to follow-up was due to the patient experiencing an adverse event.*

*The only protocol violation that resulted in study drug discontinuation was in the gatifloxacin treatment group. Patient #026-0258 was given one dose of study drug before the coordinator realized that the study had been closed to new patients.*

8.6.1.1.8 Applicant Analyses

8.6.1.1.8.1 Primary Analyses

The primary efficacy analysis was to be performed on the microbiologically evaluable patients. The distribution of the patients in the different subset populations identified above (Section 8.6.1.1.4: Study Endpoints) is summarized in the table below. It is an adaptation of Table 8.1B, from the applicant's Study Report (p. 68):

**Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients (Protocol AI420-031)**

| | Number of Patients | | |
|---|---|---|---|
| Study Population/Reason Excluded | Gatifloxacin | Ciprofloxacin | Total |
| **All Treated** | **189** | **183** | **372** |
| **Eligible** | **181** | **175** | **356** |
| **Ineligible** | **8** | **8** | **16** |
| No complicating factors | 6 | 4 | 10 |
| Did not have all of required signs/symptoms | 2 | 3 | 5 |
| Did not have pyuria | 0 | 1 | 1 |
| **Clinically Evaluable** | **93** | **96** | **189** |
| **Clinically Unevaluable** | **96** | **87** | **183** |
| Pre-treatment urine culture $<10^5$ cfu/mL | 42 | 45 | 87 |
| No Test of Cure Visit or Visit Outside Study Windows | 25 | 19 | 44 |

| | Number of Patients | | |
|---|---|---|---|
| Study Population/Reason Excluded | Gatifloxacin | Ciprofloxacin | Total |
| Uropathogen resistant | 13 | 3 | 16 |
| Less than 5 days therapy | 7 | 11 | 18 |
| Ineligible | 8 | 8 | 16 |
| Other effective antibiotics administered before Test of Cure Visit | 1 | 1 | 2 |
| **Microbiologically Evaluable** | **91** | **95** | **186** |
| **Microbiologically Unevaluable** | **98** | **88** | **186** |
| Clinically unevaluable for reasons stated above | 96 | 87 | 183 |
| Had Test of Cure Visit but no Test of Cure urine culture | 2 | 0 | 2 |
| Antibiotics for Failure before Test of Cure culture | 0 | 1 | 1 |

*Reviewer's Comments*

*The different subsets were comparable between the two treatment groups. A random sampling of the case report forms did not reveal any misrepresentation of the patients' data of such significance that patient reclassification would be warranted.*

*It is noted that a quite a few patients were considered clinically unevaluable because the pre-treatment urine culture had < $10^5$ cfu/ml. This reviewer believes that this finding is reflective of the entry criteria that were utilized for this study. In essence, a patient that had a clinical syndrome compatible with complicated urinary tract infections but a pre-treatment culture with $10^3$ or $10^4$ cfu/ml could conceivably be treated for this syndrome under the right clinical circumstances. Nevertheless, that patient would not be eligible for the efficacy analyses for this study. Furthermore, the numbers were essentially even between the two treatment groups, therefore it is not believed that this would have introduced bias into the study.*

The bacteriologic response at the Test of Cure Visit in the microbiologically evaluable patient subset is summarized in the following table is reproduced from the applicant's Study Report (Table 10.1.1A, p. 94):

**Initial Bacteriologic Response at Test of Cure Visit, Microbiologically Evaluable Patients (Protocol AI420-031)**

| Bacteriologic Response | Number (%) of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 91 | Ciprofloxacin N = 95 | Total N = 186 |
| **Total** | **91 (100)** | **95 (100)** | **186 (100)** |
| Eradication of all uropathogens[a] | 84 (92) | 79 (83) | 163 (88) |
| Persistence | 1 (1) | 8 (8) | 9 (5) |
| Superinfection | 2 (2) | 0 | 2 (1) |
| New Infection | 4 (4) | 7 (7) | 11 (6) |
| New and Superinfections | 0 | 1 (1) | 1 (1) |
| **Complicated UTI** | **66** | **75** | **141** |
| Eradication of all uropathogens[b] | 61 (92) | 62 (83) | 123 (87) |
| Persistence | 0 | 6 (8) | 6 (4) |
| Superinfection | 2 (3) | 0 | 2 (1) |
| New Infection | 3 (5) | 6 (8) | 9 (6) |
| New and Superinfections | 0 | 1 (1) | 1 (1) |
| **Pyelonephritis** | **25** | **20** | **45** |
| Eradication of all uropathogens | 23 (92) | 17 (85) | 40 (89) |
| Persistence | 1 (4) | 2 (10) | 3 (7) |
| Superinfection | 0 | 0 | 0 |
| New Infection | 1 (4) | 1 (5) | 2 (4) |
| New and Superinfections | 0 | 0 | 0 |

[a] 95% Confidence Interval: Gatifloxacin 400 mg QD vs. Ciprofloxacin 500 mg BID (-2.2%, 21.9%).
[b] 95% Confidence Interval: Gatifloxacin 400 mg QD vs. Ciprofloxacin 500 mg BID (-4.1%, 24.5%).

*Reviewer's Comments*

*The bacteriological response rates for gatifloxacin were numerically higher for the gatifloxacin treatment group. The 95% confidence interval around the difference between the point estimates of the two treatment groups would indicate that gatifloxacin was comparable to ciprofloxacin with respect to efficacy.*

8.6.1.1.8.2 Additional Analyses

The applicant evaluated the bacteriological response rate based on the pathogen identified. The following table is a reproduction of Table 10.1B in the applicant's Study Report (p. 96). It summarizes the response rate based on the pathogen.

**Bacteriologic Response of Original Uropathogen, Test of Cure Visit, Microbiologically Evaluable Patients (Protocol AI420-031)**

| | Number (%) of Isolates | | | |
|---|---|---|---|---|
| | Gatifloxacin N = 91 | | Ciprofloxacin N = 95 | |
| Pathogen[a] | Eradicated | Persisted | Eradicated | Persisted |
| **Total** | **95 (99)** | **1 (1)** | **95 (90)** | **10 (10)** |
| *E. coli* | 54 (98) | 1 (2) | 55 (96) | 2 (4) |
| *K. pneumoniae* | 11 (100) | 0 | 10 (83) | 2 (17) |
| *P. mirabilis* | 7 (100) | 0 | 2 (100) | 0 |
| *P. aeruginosa* | 0 | 0 | 5 (100) | 0 |
| *E. cloacae* | 1 (100) | 0 | 3 (100) | 0 |
| *E. faecalis* | 5 (100) | 0 | 4 (50) | 4 (50) |
| Other Gram-negative | 6 (100) | 0 | 10 (91) | 1 (9) |
| Other Gram-positive | 11 (100) | 0 | 6 (86) | 1 (14) |
| **Complicated UTI** | **71 (100)** | **0** | **76 (90)** | **8 (10)** |
| *E. coli* | 35 (100) | 0 | 40 (95) | 2 (5) |
| *K. pneumoniae* | 10 (100) | 0 | 10 (83) | 2 (17) |
| *P. mirabilis* | 6 (100) | 0 | 1 (100) | 0 |
| *P. aeruginosa* | 0 | 0 | 5 (100) | 0 |
| *E. cloacae* | 1 (100) | 0 | 3 (100) | 0 |
| *E. faecalis* | 5 (100) | 0 | 4 (57) | 3 (43) |
| Other Gram-negative | 4 (100) | 0 | 8 (89) | 1 (11) |
| Other Gram-positive | 10 (100) | 0 | 5 (100) | 0 |
| **Pyelonephritis** | **24 (96)** | **1 (4)** | **19 (90)** | **2 (10)** |
| *E. coli* | 19 (95) | 1 (5) | 15 (100) | 0 |
| *K. pneumoniae* | 1 (100) | 0 | 0 | 0 |
| *P. mirabilis* | 1 (100) | 0 | 1 (100) | 0 |
| *E. faecalis* | 0 | 0 | 0 | 1 (100) |
| Other Gram-negative | 2 (100) | 0 | 2 (100) | 0 |
| Other Gram-positive | 1 (100) | 0 | 1 (50) | 1 (50) |

[a] A patient may have more than one pathogen isolated pre-treatment.

*Reviewer's Comments*

*These data would support the applicant's claim that gatifloxacin is effective against Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis. The applicant had also requested Enterococcus faecalis, Pseudomonas aeruginosa,*

*and Enterobacter spp., however, the bacteriological data insufficient to support a claim against these pathogens.*

The applicant also evaluated gatifloxacin's response rates based on the complicating factors present at entry. These were summarized in Table 10.1.1C of the applicant's Study Report, and it is reproduced below:

**Eradication, Persistence, New or Superinfection by Complicating Factors at Test of Cure Visits, Microbiologically Evaluable Patients (Protocol AI420-031)**

| | Number (%)* of Isolates | | | | | |
|---|---|---|---|---|---|---|
| | Gatifloxacin N = 66 | | | Ciprofloxacin N = 75 | | |
| | Eradication | Persis-tence | New/Super Infections | Eradication | Persis-tence | New/Super-infections |
| **Complicating Factor** | **61 (92)** | - | **5 (8)** | **62 (83)** | **6 (8)** | **7 (9)** |
| Indwelling/Intermittent Catheter | 9 (82) | - | 2 (18) | 16 (76) | 2 (10) | 3 (14) |
| Ileal Loops | 1 (50) | - | 1 (50) | 3 (75) | - - | 1 (25) |
| Impaired Bladder Emptying | 34 (94) | - | 2 (6) | 26 (82) | 4 (12) | 2 (6) |
| Obstructive Uropathy | 10 (100) | - | - - | 8 (100) | - - | - - |
| Vesicoureteral Reflux (VUR) or Other Urologic Abnormalities (OUA)[a] | 7 (100) | - | - - | 9 (90) | - - | 1 (10) |

[a] This category does not include ileal loops.
* Pyelonephritis patients are excluded from this table.

*Reviewer's Comments*
*The response rate was comparable between the two treatment groups.*

8.6.1.1.9 FDA Analyses

The Division's analyses sought to verify the applicant's claims of efficacy. Case report forms were reviewed to verify that the data in the forms were accurately reported in the data files. Furthermore, the case report forms were also reviewed to assess whether the investigator's assessments appeared to follow clinical sense. At times when there were differences of opinion, an assessment was made as to whether the discrepancy was of such magnitude that it would have a significant impact on the results of the study.

In addition, the Division's statistical reviewer, Dr. Nancy Silliman, performed additional analyses on the data to assess the robustness of the results. For complete details, please refer to Dr. Sillliman's review. However, two tables from her review are reproduced below:

**Eradication Rates by Analysis Population**

| Analysis Population | Number Eradicated/Number of Patients (%) Gatifloxacin N = 189 | Ciprofloxacin N = 183 | 95% Confidence Interval* |
|---|---|---|---|
| All Treated Patients | 97/139 (70) | 85/129 (66) | (-7.9%, 16.4%) |
| Clinically Eligible Patients | 96/137 (70) | 85/127 (67) | (-8.8%, 15.1%) |
| Clinically Evaluable Patients | 84/93 (90) | 79/96 (82) | (-2.7%, 18.8%) |
| Microbiologically Evaluable Patients | 84/91 (92) | 79/95 (83) | (-2.2%, 21.9%) |

*For the difference in cure rates, gatifloxacin minus ciprofloxacin.

*Reviewer's comments*

*Although the primary efficacy was to be determined using the microbiologically evaluable patient population, it is useful to look at the other patient subsets. One would expect that the results of the study would be internally consistent if the results of the different patient populations were in the same direction, and preferably, of similar magnitude.*

**Stratified 95% Confidence Intervals by Analysis Population**

| Analysis Population | 95% Confidence Interval for the Difference in Eradication Rates (Gatifloxacin minus Ciprofloxacin) Stratified by Site | Stratified by Diagnosis |
|---|---|---|
| All Treated Patients | (-7.0%, 14.5%) | (-7.3%, 15.1%) |
| Clinically Eligible Patients | ---- | (-8.1%, 14.4%) |
| Clinically Evaluable Patients | ---- | (-1.9%, 17.9%) |
| Microbiologically Evaluable Patients | (-7.6%, 14.3%) | (-0.5%, 18.7%) |

*Reviewer's Comments*

*Dr. Silliman indicated in her review that the confidence intervals were calculated using a Mantel-Haenszel stratified approach. This verified the impression that there were no significant difference in outcome when the analysis was stratified by clinical site. Please refer to her review for complete details.*

Her assessment of the data helped to confirm that the applicant had shown that statistically, gatifloxacin was equivalent to ciprofloxacin in terms of efficacy, and that the results of this study were internally consistent.

*8.6.1.2 Safety Assessment*

8.6.1.2 .1 Extent of Drug Exposure

The following table is an adaptation of Table 9.1 (p. 83) from the applicant's Study Report.

**Study Drug Exposure, All Treated Patients (Study AI420-031)**

| | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 189 | Ciprofloxacin N = 183 | Total N = 372 |
| Number of Days | | | |
| Mean | 8.9 | 9.0 | 9.0 |
| Median | 10 | 10 | 10 |
| Minimum/Maximum | 1 – 11 | 1 - 12 | 1 - 12 |
| Number of Days (%) | | | |
| 1 – 4 | 19 (10) | 17 (9) | 36 (10) |
| 5 – 6 | 4 (2) | 3 (2) | 7 (2) |
| 7 | 9 (5) | 12 (7) | 21 (6) |
| 8 – 9 | 8 (4) | 7 (4) | 15 (4) |
| 10 | 146 (77) | 141 (77) | 287 (77) |
| >10 | 3 (2) | 3 (2) | 6 (2) |

*Reviewer's Comment*

*The duration of therapy was comparable between the two treatment groups. The majority of the patients were treated for 10 days. The number of patients that were treated for less than 4 days was also comparable between the two treatment groups.*

8.6.1.2.2 Adverse Events

8.6.1.2.2.1 All Causalities

The applicant tabulated all adverse events, regardless of causality. Appendix C is a table reproduced from the applicant's Study Report (Table 12.1.1, p. 122), listing the events. The table that follows is a modification of that table, listing the most frequently reported events.

**Most Frequently Reported Adverse Events, All Causality (Study AI420-031)**

| | Number (%) of Patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gatifloxacin (N = 189) | | | | Ciprofloxacin (N = 183) | | | |
| Adverse Clinical Event[a] | Related | Not Related | Not Assessed | Total | Related | Not Related | Not Assessed | Total |
| **Any adverse event** | **58 (31)** | **34 (18)** | **4 (2)** | **97 (51)** | **38 (21)** | **37 (20)** | **4 (2)** | **79 (43)** |
| Nausea | 21 (11) | 2 (1) | 1 (<1) | 24 (13) | 11 (6) | 0 | 0 | 11 (6) |
| Dizziness | 8 (4) | 4 (2) | 2 (1) | 14 (7) | 5 (3) | 0 | 0 | 5 (3) |

Indication: Complicated Urinary Tract Infections
Study AI420-031

| Adverse Clinical Event[a] | Number (%) of Patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gatifloxacin (N = 189) | | | | Ciprofloxacin (N = 183) | | | |
| | Related | Not Related | Not Assessed | Total | Related | Not Related | Not Assessed | Total |
| Diarrhea | 6 (3) | 1 (<1) | 0 | 7 (4) | 5 (3) | 4 (2) | 0 | 9 (5) |
| Pain | 0 | 5 (3) | 2 (1) | 8* (4) | 0 | 1 (<1) | 0 | 1 (<1) |
| Pain Back | 1 (<1) | 5 (3) | 0 | 6 (3) | 1 (<1) | 3 (2) | 0 | 4 (2) |
| Vomiting | 6 (3) | 0 | 0 | 6 (3) | 5 (3) | 0 | 0 | 5 (3) |
| Headache | 4 (2) | 2 (1) | 0 | 6 (3) | 6 (3) | 4 (2) | 0 | 10 (5) |
| Urinary Retention | 0 | 5 (3) | 0 | 5 (3) | 1 (<1) | 3 (2) | 0 | 4 (2) |
| Dysuria | 2 (1) | 3 (2) | 0 | 5 (3) | 1 (<1) | 10 (5) | 1 (<1) | 12 (7) |
| Pain Abdomen | 4 (2) | 1 (<1) | 0 | 5 (3) | 3 (2) | 7 (4) | 0 | 10 (5) |
| Dry Mouth | 5 (3) | 0 | 0 | 5 (3) | 0 | 0 | 0 | 0 |

[a] A patient may have more than one adverse event. Only those adverse events occurring in 2% or more of the patients in either treatment group are listed.

*For one patient, the relationship of the adverse event to study drug was not recorded.

*Reviewer's Comments*

*Overall, gatifloxacin had more adverse events reported than ciprofloxacin, and more were assessed as being study-drug related than for ciprofloxacin. These results seemed to be driven by "nausea" and "dizziness." Otherwise, the kinds of adverse events, and their incidences, were comparable between the two treatment groups.*

*Of the 19 patients that complained about dizziness, the demographic information was as follows:*

| | *Number of Patients* | |
|---|---|---|
| | *Gatifloxacin* | *Ciprofloxacin* |
| *Gender* | | |
| *Female* | *8* | *3* |
| *Male* | *6* | *2* |
| *Age (years)* | | |
| *Mean* | *67* | *39* |
| *Range* | *21-88* | *25-63* |

*In addition to the previous observation that there were more patients on the gatifloxacin treatment group that complained about dizziness, it is noted that they tended to be slightly older. The gatifloxacin group, being older, also tended to have cardiovascular medical histories, including hypertension, coronary artery*

*disease, and stable dysrythmias. These factors make it difficult to determine the contribution of the study medication to their complaints of dizziness.*

*The breakdown between gender seemed to be comparable between the two treatment groups.*

8.6.1.2.2.2 Treatment Related

The following table isolates the adverse events from the previous table that were assessed as being study drug-related by the investigator. It also identifies the degree of severity that was associated with each adverse event. It is an adaptation of Table 12.1.2 (p. 125) from the applicant's Study Report.

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## Drug Related Adverse Clinical Events, All Treated Patients (Study A1420-031)

| | Number (%) of Patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gatifloxacin (N = 189) | | | | Ciprofloxacin (N = 183) | | | |
| Adverse Clinical Event[a] | Mild | Moderate | Severe | Total | Mild | Moderate | Severe | Total |
| **Any drug-related adverse event** | **31 (16)** | **19 (10)** | **8 (4)** | **58 (31)** | **21 (11)** | **13 (7)** | **3 (2)** | **37 (20)** |
| Nausea | 14 (7) | 4 (2) | 3 (2) | 21 (11) | 4 (2) | 5 (3) | 1 (<1) | 10 (6) |
| Dizziness | 8 (4) | 0 | 0 | 8 (4) | 4 (2) | 1 (<1) | 0 | 5 (3) |
| Diarrhea | 3 (2) | 2 (1) | 1 (<1) | 6 (3) | 4 (2) | 1 (<1) | 0 | 5 (3) |
| Vomiting | 1 (<1) | 2 (1) | 3 (2) | 6 (3) | 1 (<1) | 4 (2) | 0 | 5 (3) |
| Dry Mouth | 4 (2) | 0 | 1 (<1) | 5 (3) | 0 | 0 | 0 | 0 |
| Headache | 4 (2) | 0 | 0 | 4 (2) | 5 (3) | 1 (<1) | 0 | 6 (3) |
| Somnolence | 4 (2) | 0 | 0 | 4 (2) | 1 (<1) | 0 | 0 | 1 (<1) |
| Pain Abdomen | 3 (2) | 1 (<1) | 0 | 4 (2) | 1 (<1) | 1 (<1) | 1 (<1) | 3 (2) |
| Dyspepsia | 3 (2) | 0 | 1 (<1) | 4 (2) | 3 (2) | 0 | 0 | 3 (2) |
| Flatulence | 1 (<1) | 2 (1) | 0 | 3 (2) | 1 (<1) | 0 | 0 | 1 (<1) |
| Vaginitis (% women) | 0 | 3 (2) | 0 | 3 (2) | 1 (<1) | 0 | 0 | 1 (<1) |
| Constipation | 0 | 2 (1) | 0 | 2 (1) | 0 | 0 | 0 | 0 |
| Tremor | 1 (<1) | 1 (<1) | 0 | 2 (1) | 0 | 0 | 0 | 0 |
| Vertigo | 1 (<1) | 0 | 1 (<1) | 2 (1) | 0 | 0 | 0 | 0 |
| Dysuria | 2 (1) | 0 | 0 | 2 (1) | 1 (<1) | 0 | 0 | 1 (<1) |
| Hematuria | 1 (<1) | 1 (<1) | 0 | 2 (1) | 0 | 0 | 0 | 0 |
| Insomnia | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) | 1 (<1) | 0 | 2 (1) |

[a] Only those adverse events occurring in 1% or more of the patients in either treatment group are listed here for a full listing see Appendix 16B.

*Reviewer' Comments*

*The findings were similar to before, in that there were more adverse events assessed as being study drug-related in the gatifloxacin treatment group than in the ciprofloxacin treatment group. And as before, the results were driven by the adverse events "nausea" and "dizziness." Most of the adverse events were categorized as "mild – Grade 1."*

8.6.1.2.2.3 Serious Adverse Events

The applicant reported that a total of 17 patients experienced serious adverse events. There were 10 in the gatifloxacin treatment group and 7 in the ciprofloxacin treatment group. Of the 10 patients in the gatifloxacin arm, there were 2 that were assessed by the investigator as having experienced events with causality assigned to the study drug. In the ciprofloxacin arm, there was one.

The table on the next page is an adaptation of Table 12.3 (p. 129) in the applicant's Study Report, and summarizes the types of serious adverse events that were reported, as well as their investigator-assessed relationship.

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## Serious Adverse Clinical Events of All Causes, All Treated Patients (Study AI420-031)

| | Number (%) of Patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gatifloxacin (N = 189) | | | | Ciprofloxacin (N = 183) | | | |
| Adverse Clinical Event | Related | Not Related | Not[a] Assessed | Total | Related | Not Related | Not Assessed | Total |
| **Any serious event** | **2 (1)** | **7 (4)** | **1 (<1)** | **10 (5)** | **1 (<1)** | **6 (3)** | **0** | **7 (4)** |
| Congestive heart failure | 0 | 1 (<1) | 1 (<1) | 2 (1) | 0 | 0 | 0 | 0 |
| Multiple Sclerosis | 0 | 2 (1) | 0 | 2 (1) | 0 | 0 | 0 | 0 |
| Pneumonia | 1 (<1) | 1 (<1) | 0 | 2 (1) | 0 | 0 | 0 | 0 |
| Vomiting | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Palpitation | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Nausea | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Convulsion | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Abnormal thinking | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Hyperplasia Adrenal Cortex | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Hernia | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Infection | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Sepsis | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Disorder Lung | 0 | 1 (<1) | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Infection Urinary Tract | 1 (<1) | 0 | 0 | 1 (<1) | 0 | 0 | 0 | 0 |
| Pain Chest | 0 | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Appendicitis | 0 | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Pain Abdomen | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 0 | 1 (<1) |
| Fracture Bone | 0 | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Dyspnea | 0 | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Cystitis | 0 | 0 | 0 | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| Pregnancy | 0 | 0 | 0 | 0 | 0 | 2 (1) | 0 | 2 (1) |

[a] The relationship to study treatment was not recorded.

*Reviewer's Comments*

*There were two patients in the gatifloxacin treatment group that experienced serious adverse events assessed as being "related" to the study drug:*

*Patient #005-0121 was an 85 year-old white female enrolled with a diagnosis of complicated UTI. She had a history of peripheral vascular disease (was s/p carotid endarterectomy), hypertension, and "irregular heart beat," for which she was taking atenolol and digoxin, respectively. She experienced nausea and vomiting, graded as severe (Grade II), that began about a day after initiating therapy and continued for about 2 weeks. The causality assessment by the investigator was "probable" and the study medication was discontinued. The case report form also revealed that this patient experienced mild (grade I) dizziness approximately 5 days after she had begun to experience nausea and vomiting. The causality assessment for the dizziness was reported as "unassessable" by the investigator. She was hospitalized for treatment with intravenous fluids for presumed dehydration. Although it is presumed that an electorcardiogram was performed upon admission to the hospital, the case report form did not report its result.*

*Patient #015-0242 was an 86 year old white female enrolled with a diagnosis of complicated UTI. She experienced pneumonia, superinfection, and altered mental status that began within the week after having begun therapy. The severity was assessed by the investigator as moderate (Grade II), and the causality was "possible."*

*Review of the SAS transport data files identified four additional patients who apparently experienced serious adverse events. Following is a brief synopsis of each patient, obtained after review of the case report forms:*

***Gatifloxacin***

*Patient #004-0274: 83 year-old white female enrolled with the diagnosis of a complicated UTI. She was treated from 2/10/98 to 3/5/98. She completed the course without incident. She was hospitalized after a syncopal episode on 3/22/98. The episode was deemed to due to congestive heart failure (CHF) and unrelated to study drug by the investigator; patient had a history of CHF and hypertension.*

*Patient #017-0127: 87 year-old white female enrolled with the diagnosis of a complicated UTI. She was treated from 12/5/97 till about 12/15/97, and had an evaluation of "cured" on 12/16/97. She was hospitalized from 1/16/98 till 1/19/98 with a diagnosis of right lower lobe pneumonia. The pneumonia was assessed as being unrelated to the study drug by the investigator. She also had a past medical history of severe coronary disease and congestive heart failure.*

*Patient #035-0342: 53 year-old white female enrolled with the diagnosis of a complicated UTI. She was treated from 1/23/98 until 2/6/98. On 1/30/98 she presented with new-onset hyperglycemia (672 mg/dL). She had a past medical history of a renal transplant and was taking prednisone, cyclosporine and imuran. The causality assessment by the investigator was classified as "unrelated."*

***Ciprofloxacin***

*Patient #007-0017: 84 year-old white female enrolled with the diagnosis of a complicated UTI. She was treated from 9/4/97 until 9/18/97. She died on 10/18/97; her death was assessed as being unrelated to the study drug by the investigator. She had a past medical history of left temporal lobe infarction and progressive dementia.*

*Review of the case report forms did not reveal any additional information that would suggest changing the investigator's assessment. It is this reviewer's conclusion that these serious adverse events should have been reported by the applicant in their summary table, however, in view of the fact that they appeared to be unrelated to the study drug, their omission is not believed to be critical.*

8.6.1.2.2.4 Severe and Life-threatening Events

There were no severe and life-threatening adverse events reported for this study.

8.6.1.2.2.5 Discontinuation from Studies

8.6.1.2.2.5.1 Discontinuations Due to Adverse Events

The following table summarizes the number of patients that were discontinued due to adverse events, and the types of adverse events that were observed. It is adapted from Table 12.4 (p. 131) in the applicant's Study Report.

**Discontinuation of Study Medication Due to Adverse Clinical Events, All Treated Patients (Study AI420-031)**

| | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 189 | Ciprofloxacin N = 183 | Total N = 372 |
| Number Discontinued[a] | 12 | 10 | 22 |
| Adverse Events[b] | | | |
| Nausea | 5 (5)[c] | 5 (5) | 10 (10) |
| Vomiting | 4 (4) | 3 (3) | 7 (7) |
| Diarrhea | 2 (2) | 0 | 2 (2) |
| Dizziness | 1 (0) | 2 (2) | 3 (2) |

| | | | |
|---|---|---|---|
| Pain Abdomen | 1 (1) | 1 (1) | 2 (2) |
| Insomnia | 1 (1) | 1 (1) | 2 (2) |
| Headache | 0 | 2 (2) | 2 (2) |

[a] Only events that occurred in 2 or more patients are included in this table.

[b] Patients may be included in one or more adverse clinical event.

[c] ( ) = (# that were drug related).

*Reviewer's Comments*

*It is noted that the number of patients that were discontinued from study drug because of a particular adverse event was comparable between the two treatment groups. These data must be taken in the context of the two previous tables however, which illustrated that more patients on the gatifloxacin treatment group experienced adverse events than in the ciprofloxacin treatment arm.*

8.6.1.2.2.5.2 Discontinuations Due to Laboratory Abnormalities

The protocol contained guidelines to help determine when a patient should have study drug adjustments. They were derived from the National Cancer Institute's Common Toxicity Criteria (CTC) and the Acquired Immune Deficiency Syndrome (AIDS) Clinical Trials Group (ACTG) classification of laboratory abnormalities and are reproduced from the applicant's study protocol (p. 54) in the following table:

Toxicity Grades for Specific Laboratory Tests (Study AI420-031)

| | | Grade[a] | | | | |
|---|---|---|---|---|---|---|
| Laboratory Test | Event | 0 | 1 | 2 | 3 | 4 |
| Hemoglobin (g/dL)[b] | Anemia | LNL[c] | 10.1 - <LNL | 8.0 - 9.9 | 6.5 – 7.9 | <6.5 |
| Platelet Count (x10[3] cells/uL)[b] | Thrombocytopenia | LNL | 75 - <LNL | 50 - 74 | 25 – 49 | <25 |
| Leukocyte Count (x10[3] cells uL)[b] | Leukopenia | 4.0 | 3.0 - 3.9 | 2.0 - 2.9 | 1.0 – 1.9 | <1.0 |
| Neutrophil Count[b] | Neutropenia | 2000 | 1500 – 1999 | 1000 - 1499 | 500 – 999 | <500 |
| Blood Urea Nitrogen (BUN) (mg dL)[b] | Elevated BUN | 1.25 x UNL[d] | 1.26 - 2.5 x UNL | 2.6 - 5.0 x UNL | 5.1 – 10.0 x UNL | >10.0 x UNL |
| Urea (mmol L)[b] | Elevated Urea | 1.25 x UNL | 1.26 - 2.5 x UNL | 2.6 - 5.0 x UNL | 5.1 – 10.0 x UNL | >10.0 x UNL |
| Creatinine (mg dL)[b] | Elevated creatinine | UNL | 1.1 – 1.5 x UNL | 1.6 - 3.0 x UNL | 3.1 - 6.0 x UNL | >6.0 x UNL |
| AST(SGOT), ALT(SGPT), Alkaline Phosphatase (U/L)[b] | Abnormal liver function | UNL | 1.1 - 2.5 x UNL | 2.6 - 5.0 x UNL | 5.1 – 20.0 x UNL | >20.0 x UNL |
| Total Bilirubin (mg dL)[b] | Hyperbilirubinemia | UNL | - - - | 1.1 - 1.4 x UNL | 1.5 - 3.0 x UNL | >3.0 xUNL |
| Amylase (U/L)[b] | Hyperamylasemia | UNL | 1.1 - 1.5 x UNL | 1.6 - 2.0 x UNL | 2.1 - 5.0 x UNL | >5.0 x UNL |
| Glucose (mg dL)[b,] | Hypoglycemia or Hyperglycemia | 65 - 115 | 55 – 64 or 116 – 160 | 40 – 54 or 161 - 250 | 30 – 39 or 251 – 500 | <30 or >500 |
| Sodium (mEq/L)[b] | Hyponatremia or Hypernatremia | 136 – 145 | 130 – 135 or 146 – 150 | 123 – 129 or 151 – 157 | 116 – 122 or 158 – 165 | <116 or >165 |

| | | | | | | |
|---|---|---|---|---|---|---|
| assium (mEq/L)[c] | Hypokalemia or Hyperkalemia | 3.5 – 5.5 | 3.0 – 3.4 or 5.6 – 6.0 | 2.5 - 2.9 or 6.1 - 6.5 | 2.0 - 2.4 or 6.6 – 7.0 | <2.0 or >7.0 |
| Chloride (mEq/L)[c] | Hypochloremia or Hyperchloremia | 95 - 110 | 92 – 94 or 111 – 113 | 89 – 91 or 114 - 116 | 86-88 or 117 – 119 | < 86 or >119 |
| Bicarbonate (mEq/L)[c] | Acidosis or Alkalosis | 22.0 - 29.9 | 18.0 – 21.9 or 30.0 – 33.9 | 14.0 - 17.9 or 34.0 - 37.9 | 10.0 – 13.9 or 38.0 – 41.9 | <10.0 or >41.9 |

a Grades were based on CTC[1] and ACTG[1] Scales or were established by Sponsor.[f]

b Glucose grade to be attached to result of fasting specimen only. . .

c LNL – Lower Limit of Normal.

d UNL – Upper Limit of Normal.

*Reviewer's Comments*

*One patient from each treatment group was discontinued from study drug because of an abnormal baseline laboratory value. In both cases, a baseline elevated creatinine was not recognized until at least two doses of study mediation were given (Gatifloxacin patient #016-0072, and ciprofloxacin patient #026-0156).*

*Of the patients that had deviations from normal pre-treatment laboratory values, most were mild in severity. There were 5 patients that had Grade 3 or 4 toxicity (3 gatifloxacin patients, 2 ciprofloxacin patients). None of the gatifloxacin patients discontinued their study drug because of the abnormal laboratory value.*

*Of the patients that had abnormal pre-treatment values worsened while on therapy, 3 patients in each treatment group had a worsening to Grade 3, and one patient in the gatifloxacin treatment group had a worsening to Grade 4. None of the gatifloxacin patients that manifested Grade 3 toxicity had their study drug discontinued; the patient who had Grade 4 toxicity completed 8 out of 10 days of therapy.*

8.6.1.2.2.6 Assessment of Drug Relationship for Selected Adverse Events

The SAS transport data files were analyzed in an attempt to evaluate whether there was a correlation between abnormal laboratory values and study drug administration. Of particular interest were hepatic enzyme and serum amylase elevations.

8.6.1.2.2.6.1 Hepatobiliary System Abnormalities

There were 18 patients that experienced an elevation of serum total bilirubin while on therapy (14 gatifloxacin and 4 ciprofloxacin patients). The clinical scenario of concern was an elevation in serum total bilirubin from normal pre-treatment values, accompanied by elevated serum ALT levels.

Of the 14 gatifloxacin patients that had elevated total bilirubin while on therapy, 6 had normal pre-treatment values. Of these 6 patients, 5 had normal hepatic transaminases. The sixth patient did have elevated transaminases while on therapy, however, he also had elevated transaminases before starting treatment.

In conclusion, no correlation could be made between elevated liver enzyme and gatifloxacin therapy.

8.6.1.2.2.6.2 Pancreatic Enzyme Abnormalities

There were 20 patients who developed elevated serum amylases while on therapy (8 gatifloxacin and 12 ciprofloxacin). Of the 8 gatifloxacin patients, 4 had normal baseline values. The increases observed in these four patients ranged from 23 to 814 U/L (mean = 264), but there was one patient that had an increase of 814 U/L. Without this patient, the range was 23 to 125 U/L, with a mean of 82 U/L. It was noted that 3 of the 4 patients in this group were females, and that 3 of the 4 patients also had an elevated serum creatinine reported during the study:

1. Patient #007-0077 – see below
2. Patient #0170126 – 85 year-old white female, had an elevated creatinine of about 1.5 mg/dL throughout the study, and manifested a mild increase in serum amylase to 119 U/L.
3. Patient ##030-0302 – 94 year old male, had an elevated creatinine of 1.7 mg/dL throughout the study, and had a mild elevation in serum amylase to 104 U/L.

None of the gatifloxacin patients complained of abdominal pain associated with the abnormal serum amylase. It is possible that the asymptomatic elevation in serum creatinine may have been in part due to mild renal insufficiency.

The patient that manifested such a dramatic increase in serum amylase (Patient #007-0077) was an 85 year-old white female resident of a nursing home enrolled with a diagnosis of complicate UTI. She had a past medical history significant for hypertension, melena, vasovagal syncope, osteoarthritis, and depression. Her serum amylase increased on Day 20 to 864 U/L from a baseline value of 50 U/L. She completed her 10 course of therapy without any problems. The applicant noted that this patient also had other abnormal laboratory values, including serum creatinine to 2.3 mg/dL (from a baseline of 0.9 mg/dL), but was clinically asymptomatic, hypothesizing that perhaps the laboratory tests belong to another resident of the home.

Of interest is that in the patients that had abnormal pre-treatment values, 3 out 4 had a decrease in their serum amylase values while on therapy, the 4th patient's serum amylase remained about the same.

In conclusion, the observed elevations in serum amylase tended to be mild, asymptomatic, primarily in the elderly, and perhaps reflective of an elevated serum creatinine. There did not appear to be any correlation between increased serum amylase levels and gatifloxacin therapy.

8.6.1.2.2.7 Mortality Experience

One death was reported in the study. Patient #007-0017, in the ciprofloxacin treatment group, had a history of progressive dementia due to a cerebrovascular accident. The

death, on Day +35, was assessed as being unrelated to study medication by the investigator.

*Reviewer's Comments*
*Review of the case report form did not reveal any additional information to reject the investigator's assessment.*



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## 8.6.2 Protocol AI420-011: A Randomized, Double-Blind, Mulitcenter, Phase II/III Comparison of Gatifloxacin to Ciprofloxacin in the Treatment of Complicated Urinary tract Infection and Pyelonephritis

### *8.6.2.1 Efficacy Evaluation*

8.6.2.1.1 Study Design and Objectives

The study design and objectives were identical to the ones in Study AI420-031. One significant difference was that this study included 5 clinical sites in Canada, and was therefore not a completely domestic study. Appendix D contains is a list of the investigators that were involved in this study.

*Reviewer's Comment*

*As noted above, there were 5 Canadian clinical investigators involved in this study, and therefore this study could be said to have contained data from foreign sites. In such circumstances, it is important to assess whether conclusions derived from such data can be extrapolated to the United States' population. Questions that must be addressed include:*

1) *Is the clinical presentation (and/or clinical progression) of the disease comparable to what would be expected in the United States' patients?*
2) *Is the clinical management of the patients comparable to what was being done in the United States sites?*
3) *What is the relative contribution of the "foreign data" to the overall database of the study?*

*This reviewer believes that there are no significant differences between the Canadian and the U.S. clinical sites, either in the clinical presentation and/or disease progression, nor in the general clinical management, that would preclude utilization of these data. Furthermore, it is also noted that the overall contribution from the Canadian sites was not of a quantity that would be expected to have undue influence on the overall results of the study. For Study AI420-011, the number Canadian patients involved was as follows:*

| *Number of Canadian Subjects/ Number of Subjects in the Study* | | | |
|---|---|---|---|
| *Randomized* | *Treated* | ***Clinically Eligible*** | ***Microbiologically Eligible*** |
| *28 354 (8%)* | *28 350 (8%)* | *27/340 (8%)* | *16/180 (9%)* |

*Therefore, it is this reviewer's conclusion that the data from both studies can, for all practical purposes, be analyzed together.*

8.6.2.1.2 Eligibility Criteria

The inclusion and exclusion criteria were essentially the same as for Study AI420-031.

*Reviewer's Comment:*

*Ten patients had deviations from the enrollment criteria. They are summarized below, in a table adapted from Table 7.3 in the applicant's Study Report (p. 62).*

***Protocol Violations of Enrollment Criteria (Study AI420-011)***

| | Number of Patients | | |
|---|---|---|---|
| *Violation* | *Gatifloxacin N = 173* | *Ciprofloxacin N = 181* | *Total N = 354* |
| *No complicating factors* | *3* | *5* | *8* |
| *Did not have all of required signs/symptoms* | *1* | *0* | *1* |
| *Epididymitis* | *1* | *0* | *1* |
| *TOTAL* | *5* | *5* | *10* |

*Overall, there were fewer patients in this study that were enrolment criteria violations. The largest group was "no complicating factors," and the patients were from various clinical centers.*

*As before, none of these patients were considered clinically evaluable, and therefore, were not included in any of the efficacy analyses.*

8.6.2.1.3 Study Drugs and Randomization Methods

Randomization procedures and study drug distribution were similar to Study AI420-031.

*Reviewer's Comments*

*Previous comments regarding the randomization procedure utilized also apply to this study. Please refer to Section 8.6.1.13 of this review, as well as Dr. Nancy Stillman's review, for details about the implications of this method.*

8.6.2.1.4 Study Endpoints

The study endpoints were the same as in Study AI420-031.

8.6.2.1.5 Termination and Clinical Follow-up

Termination and clinical follow-up were the same as in Study AI420-031.

8.6.2.1.6 Sample Size and Statistical Plan

The sample size calculations and statistical plan were the same as for Study AI420-031.

8.6.2.1.7 Study Results

8.6.2.1.7.1 Enrollment and Description of Patients Enrolled in the Study

During the time period from 27 July 1997 to 3 June 1998, 354 patients were randomized; 350 received at least one dose of study drug. The following table, reproduced from the applicant's study report (Table 8.1A, p. 65), indicate the patient enrollment by site, as well as the number that were clinically and microbiologically evaluable.

**Patient Enrollment, by Investigator (Study AI420-011)**

| | | Number (%) of Patients | | | |
|---|---|---|---|---|---|
| Site/Investigator | | Number Randomized | Number Treated | Number Clinically Eligible | Microbiologically Evaluable |
| 004 | I. Klimberg, M.D. | 41 (100) | 40 (98) | 39 (95) | 22 (54) |
| 006 | J. Young, M.D. | 36 (100) | 36 (100) | 36 (100) | 16 (44) |
| 007 | W. Wells, M.D. | 36 (100) | 35 (97) | 32 (89) | 14 (39) |
| 018 | S. Childs, M.D. | 29 (100) | 29 (100) | 28 (97) | 19 (66) |
| 014 | R. Feldman, M.D. | 23 (100) | 22 (96) | 22 (96) | 11 (48) |
| 012 | P. Knapp, M.D. | 20 (100) | 20 (100) | 19 (95) | 9 (45) |
| 021 | N. Zinner, M.D. | 20 (100) | 20 (100) | 20 (100) | 10 (50) |
| 022 | C. Brito, M.D. | 20 (100) | 20 (100) | 19 (95) | 10 (50) |
| 011 | D. Saltzstein, M.D. | 19 (100) | 19 (100) | 18 (95) | 9 (47) |
| 019 | C. Steidle, M.D. | 19 (100) | 19 (100) | 19 (100) | 12 (63) |
| 020 | J. Tuttle, M.D. | 16 (100) | 16 (100) | 16 (100) | 13 (81) |
| 013 | J. McMurray, M.D. | 15 (100) | 15 (100) | 15 (100) | 10 (67) |
| 028 | L. Nicolle, M.D. | 10 (100) | 10 (100) | 10 (100) | 6 (60) |
| 015 | J. Kaufman, M.D. | 8 (100) | 8 (100) | 7 ((88) | 2 (25) |
| 008 | E. Dula, M.D. | 7 (100) | 6 (86) | 6 (86) | 2 (29) |
| 026 | J. Grantmyre, M.D. | 7 (100) | 7 (100) | 6 (86) | 1 (14) |
| 005 | M. Gittleman, M.D. | 5 (100) | 5 (100) | 5 (100) | 1 (20) |
| 024 | D. Grimard, M.D. | 5 (100) | 5 (100) | 5 (100) | 4 (80) |
| 029 | T. Louie, M.D. | 5 (100) | 5 (100) | 5 (100) | 4 (80) |
| 017 | M. Ratner, M.D. | 3 (100) | 3 (100) | 3 (100) | 0 (0) |
| 023 | J. Snyder, M.D. | 3 (100) | 3 (100) | 3 (100) | 1 (33) |
| 009 | J. Susset, M.D. | 2 (100) | 2 (100) | 2 (100) | 0 (0) |
| 010 | D. Winchester, M.D. | 2 (100) | 2 (100) | 2 (100) | 2 (100) |
| 016 | H. Padma-Nathan, M.D. | 2 (100) | 2 (100) | 2 (100) | 1 (50) |
| 030 | C St. Pierre, M.D. | 1 (100) | 1 (100) | 1 (100) | 1 (100) |

| Site/Investigator | Number (%) of Patients | | | |
|---|---|---|---|---|
| | Number Randomized | Number Treated | Number Clinically Eligible | Microbiologically Evaluable |
| Total | 354 (100) | 350 (99) | 340 (96) | 180 (51) |

*Reviewer's Comment:*
*There was no clinical site that had an undue number of patients not receive study drug, nor be clinically evaluable. The number of patients that were deemed microbiologically evaluable however, varied widely among the centers.*

The following table, adapted from the applicant's Study Report (Table 8.3, p. 69), and the Integrated Summary and Safety Report (Table 7.2, p. 332), summarizes the demographic characteristics of the patient population:

**Demographic Characteristics, All treated Patients (Study AI420-011)**

| Characteristic | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 170 | Ciprofloxacin N = 180 | Total N = 350 |
| Gender | | | |
| Female (%) | 84 (49) | 93 (52) | 177 (51) |
| Male (%) | 86 (51) | 87 (48) | 173 (49) |
| Race | | | |
| White (%) | 154 (91) | 158 (88) | 312 (89) |
| Black (%) | 7 (4) | 9 (5) | 16 (5) |
| Hispanic (%) | 4 (2) | 13 (7) | 17 (5) |
| Asian (%) | 2 (1) | 0 - | 2 (<1) |
| Other (%) | 3 (2) | 0 - | 3 (<1) |
| Age (years) | | | |
| Mean | 64 | 61 | 63 |
| Median | 68 | 66 | 67 |
| Range | 22 - 95 | 18 – 95 | 18 - 95 |
| < 65 | 72 (42) | 86 (48) | 158 (45) |
| 65 – 74 | 43 (25) | 41 (23) | 84 (24) |
| ≥ 75 | 55 (32) | 53 (29) | 108 (31) |

*Reviewer's Comment:*
*As with Study AI420-031, the majority of the patient population was white, however, there was a more even distribution with respect gender than in the other study.*

*It was also noted that although the range of the patients' ages were similar between the two studies, the mean and median for Study AI420-011 was older than for the other study.*

8.6.2.1.7.2 Patient Diagnoses and Complicating Factors at Entry

Types of diagnoses and duration of infection are summarized in the following table, which is adapted from Table 8.4C (p. 73) in the applicant's Study Report.

**Disease Diagnoses, All Treated Patients (Study AI420-011)**

| | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 170 | Ciprofloxacin N = 180 | Total N = 350 |
| Diagnosis | | | |
| Complicated UTI (%) | 162 (95) | 168 (93) | 330 (94) |
| Pyelonephritis (%) | 8 (5) | 12 (7) | 20 (6) |
| Duration of Infection (days)[a] | | | |
| Mean | 9.9 | 10.4 | 10.1 |
| Median | 5 | 5 | 5 |
| Minimum – Maximum | 1 - 90 | 1 – 120 | 1 - 120 |

[a] Two patients in the gatifloxacin group (-022-206, -022-602) had no recorded duration of infection.

*Reviewer's Comment*
*The distribution of diagnoses and duration of infection was comparable between the two treatment groups. However, this study did not enroll as many patients with the diagnosis of "pyelonephritis" as in Study AI420-031.*

Complicating factors

The applicant evaluated the types, and number, of complicating factors that were present upon study entry. The table below is an adaptation of Table 8.4D (p. 75) from the applicant's Study Report:

## Complicating Factors at Study Entry, All Treated Patients (Study AI420-011)

| | Number of Patients (%)* | | |
|---|---|---|---|
| | Gatifloxacin N = 162 | Ciprofloxacin N = 168 | Total N = 330 |
| **No Complicating Factor** | 3 (2) | 5 (3) | 8 (2) |
| **One Complicating Factor** | 124 (76) | 119 (71) | 243 (74) |
| Impaired Bladder Emptying | 51 (31) | 46 (26) | 97 (29) |
| Vesicoureteral Reflux (VUR) or Other Urologic Abnormalities (OUA)[a] | 40 (25) | 36 (21) | 76 (23) |
| Obstructive Uropathy | 16 (10) | 18 (11) | 34 (10) |
| Indwelling/Intermittent Catheter | 10 (6) | 12 (7) | 22 (7) |
| Ileal Loops | 7 (4) | 7 (4) | 14 (4) |
| **More Than One Complicating Factor** | 35 (22) | 44 (26) | 79 (24) |
| Indwelling/Intermittent Catheter **plus**: | 20 (12) | 30 (18) | 50 (15) |
| Impaired Bladder Emptying | 15 (9) | 24 (14) | 39 (12) |
| VUR or OUA | 4 (2) | 2 (1) | 6 (2) |
| Obstructive Uropathy | 1 (1) | 3 (2) | 4 (1) |
| Impaired Bladder Emptying **plus**: VUR or OUA | 0 | 1 (1) | 1 (<1) |
| Ileal Loops **plus**: | 0 | 6 (4) | 6 (2) |
| Impaired Bladder Emptying | 0 | 1 (1) | 1 (<1) |
| VUR or OUA | 0 | 4 (2) | 4 (1) |
| Indwelling/Intermittent Catheter | 0 | 1 (1) | 1 (<1) |
| Impaired Bladder Emptying **plus**: | 10 (6) | 5 (3) | 15 (5) |
| VUR or OUA | 7 (4) | 3 (2) | 10 (3) |
| Obstructive Uropathy | 2 (1) | 1 (1) | 3 (1) |
| Obstructive Uropathy **plus** VUR or OUA | 1 (1) | 1 (1) | 2 (1) |
| Obstructive Uropathy **plus** VUR or OUA | 5 (3) | 3 (2) | 8 (2) |

[a] This category does not include Ileal Loops.
* Pyelonephritis patients are excluded from this table.

*Reviewer's Comment*

*As with the other study, there are instances where there are examples of numerical differences in one arm vs. another in certain categories. For example, there were more patients in the gatifloxacin treatment group with impaired bladder emptying, while there were more patients in the ciprofloxacin treatment group with ileal loops plus another complicating factor. Clinically meaningful*

*differences did not exist between the treatment arms, therefore, the overall impression is as before: the two treatment groups were comparable with respect to the number of complicating factors that were present at entry.*

8.6.2.1.7.3 Patient Disposition

The following table is adapted from the applicant's Study Report (Table 9.2, p.84):

**Reason for Discontinuation of Study Medication (Study AI420-011)**

| | Number (%) of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 170 | Ciprofloxacin N = 180 | Total N = 350 |
| **Discontinued Therapy Early** | 28 (16) | 32 (18) | 60 (17) |
| Adverse Event | 17 (10) | 16 (9) | 33 (9) |
| Pathogen Resistant to Therapy | 5 (3) | 5 (3) | 10 (3) |
| Lost to Follow-Up | 2 (1) | 2 (1) | 4 (1) |
| Elevated Serum Creatinine | 2 (1) | 1 (<1) | 3 (<1) |
| Patient Request | 1 (<1) | 2 (1) | 3 (<1) |
| No Pathogen Isolated | 0 | 3 (2) | 3 (<1) |
| Other Antibiotic Given Before TOC Visit | 0 | 3 (2) | 3 (<1) |
| Patient Died | 1 (<1) | 0 | 1 (<1) |

*Reviewer's Comments*

*As with Study AI420-031, the largest proportion of patients were identified as discontinuing because they experienced an adverse event, but this number was higher in this study. However, it is noted that the rates within Study AI420-011 were comparable between the two treatment groups. In fact, in contrast to Study AI420-031, the incidences for study drug discontinuations for the different categories were generally comparable between the two treatment groups.*

*As was seen in Study AI420-031, there were more females discontinued due to adverse events in the gatifloxacin treatment group, but unlike the other study, the difference was significantly higher (16 females vs. 1 male) in this study. Furthermore, this relationship was not mirrored in the ciprofloxacin treatment group as much as it was in the other study, for there were 10 females vs. 6 males discontinued for adverse events. There is no apparent explanation for this finding. As in the other study, there was no propensity within a treatment group with respect to age or ethnic group.*

*The primary type of adverse event that was given for discontinuation from gatifloxacin therapy was nausea and vomiting – reported by 13 of the 16 female patients.*

*Finally, it is noted that compared to the other study, fewer patients were discontinued because of loss to follow-up.*



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8.6.2.1.8 Applicant Analyses

8.6.2.1.8.1 Primary Analyses

The distribution of patients in the different subset populations are summarized below (reproduced from Table 8.1B on p. 67 of the applicant's Study Report):

**Distribution of Patients in Study Populations and Reasons for Exclusion, All Treated Patients (Protocol AI420-011)**

| | Number of Patients | | |
|---|---|---|---|
| Study Population/Reason Excluded | Gatifloxacin | Ciprofloxacin | Total |
| **All Treated** | **170** | **180** | **350** |
| **Eligible** | **165** | **175** | **340** |
| **Ineligible** | **5** | **5** | **10** |
| No complicating factors | 3 | 5 | 8 |
| Did not have all of required signs/symptoms | 1 | 0 | 1 |
| Epididymitis | 1 | 0 | 1 |
| **Clinically Evaluable** | **88** | **97** | **185** |
| **Clinically Unevaluable** | **82** | **83** | **165** |
| Pre-treatment urine culture $<10^5$ cfu/mL | 38 | 39 | 77 |
| No Test of Cure Visit or visit outside study windows | 15 | 13 | 28 |
| Uropathogen resistant | 12 | 13 | 25 |
| Less than 5 days therapy | 11 | 8 | 19 |
| Ineligible | 5 | 5 | 10 |
| Other effective antibiotics administered before Test of Cure Visit | 1 | 5 | 6 |
| **Microbiologically Evaluable** | **86** | **94** | **180** |
| **Microbiologically Unevaluable** | **84** | **86** | **170** |
| Clinically unevaluable for reasons stated above | 82 | 83 | 165 |
| Had Test of Cure Visit but no Test of Cure urine culture | 2 | 3 | 5 |

*Reviewer's Comments*

*Although there were numerical differences, the two treatment arms were generally comparable to each other.*

As in Study AI420-031, the primary efficacy analysis was the bacteriologic response at the Test of Cure Visit in the microbiologically evaluable patients. The following table is reproduced from the applicant's Study Report (Table 10.1.1A, p. 94):

**Initial Bacteriologic Response at Test of Cure Visit, Microbiologically Evaluable Patients (Protocol AI420-011)**

| | Number of Patients (%) | | |
|---|---|---|---|
| Bacteriologic Response | Gatifloxacin N = 86 | Ciprofloxacin N = 94 | Total N = 180 |
| **Total** | **86 (100)** | **94 (100)** | **180 (100)** |
| Eradication of all uropathogens[a] | 71 (83) | 78 (83) | 149 (83) |
| Persistence | 5 (6) | 4 (4) | 9 (5) |
| Superinfection | 0 | 2 (2) | 2 (1) |
| New Infection | 10 (12) | 8 (9) | 18 (10) |
| New and Superinfections | 0 | 2 (2) | 2 (1) |
| **Complicated UTI** | **81** | **86** | **167** |
| Eradication of all uropathogens[b] | 67 (83) | 70 (81) | 137 (82) |
| Persistence | 4 (5) | 4 (5) | 8 (5) |
| Superinfection | 0 | 2 (2) | 2 (1) |
| New Infection | 10 (12) | 8 (9) | 18 (11) |
| New and Superinfections | 0 | 2 (2) | 2 (1) |
| **Pyelonephritis** | **5** | **8** | **13** |
| Eradication of all uropathogens | 4 (80) | 8 (100) | 12 (92) |
| Persistence | 1 (20) | 0 | 1 (8) |
| Superinfection | 0 | 0 | 0 |
| New Infection | 0 | 0 | 0 |
| New and Superinfections | 0 | 0 | 0 |

a 95% Confidence Interval: Gatifloxacin 400 mg QD vs. Ciprofloxacin 500 mg BID (-14.5%,+12.4%).
b 95% Confidence Interval: Gatifloxacin 400 mg QD vs. Ciprofloxacin 500 mg BID (-12.4%,+16.0%).

*Reviewer's Comment:*
*The bacteriological response rates are supportive of the claim that gatifloxacin was comparable to ciprofloxacin in terms of efficacy for complicated urinary tract infections. This study did not have enough patients with the diagnosis of pyelonephritis to stand alone, however, it was supportive of Study AI420-031.*

8.6.2.1.8.2 Additional Analyses

As in Study AI420-03, the applicant also performed analyses on response rate based on baseline pathogen and complicating factors.

The first table summarizes the response rate based on pathogen and is a reproduction of Table 10.1.1B in the applicant's Study Report (p. 96).

**Bacteriologic Response of Original Uropathogen, Test of Cure Visit, Microbiologically Evaluable Patients (Protocol AI420-011)**

| | Number (%) of Isolates | | | |
|---|---|---|---|---|
| | Gatifloxacin N = 86 | | Ciprofloxacin N = 94 | |
| Pathogen[a] | Eradicated | Persisted | Eradicated | Persisted |
| **Total** | **94 (95)** | **5 (5)** | **99 (96)** | **4 (4)** |
| *E. coli* | 38 (97) | 1 (3) | 48 (100) | 0 |
| *K. pneumoniae* | 10 (91) | 1 (9) | 15 (88) | 2 (12) |
| *P. mirabilis* | 4 (100) | 0 | 6 (100) | 0 |
| *P. aeruginosa* | 5 (83) | 1 (17) | 1 (100) | 0 |
| *E. cloacae* | 4 (100) | 0 | 2 (100) | 0 |
| *E. faecalis* | 3 (100) | 0 | 6 (86) | 1 (14) |
| Other Gram-negative | 17 (94) | 1 (6) | 11 (100) | 0 |
| Other Gram-positive | 13 (93) | 1 (7) | 10 (91) | 1 (9) |
| **Complicated UTI** | **90 (96)** | **4 (4)** | **91 (96)** | **4 (4)** |
| *E. coli* | 34 (100) | 0 | 41 (100) | 0 |
| *K. pneumoniae* | 10 (91) | 1 (9) | 15 (88) | 2 (12) |
| *P. mirabilis* | 4 (100) | 0 | 6 (100) | 0 |
| *P. aeruginosa* | 5 (83) | 1 (17) | 1 (100) | 0 |
| *E. cloacae* | 4 (100) | 0 | 2 (100) | 0 |
| *E. faecalis* | 3 (100) | 0 | 6 (86) | 1 (14) |
| Other Gram-negative | 17 (94) | 1 (6) | 10 (100) | 0 |
| Other Gram-positive | 13 (93) | 1 (7) | 10 (91) | 1 (19) |
| **Pyelonephritis** | **4 (80)** | **1 (20)** | **8 (100)** | **0** |
| *E. coli* | 4 (80) | 1 (20) | 7 (100) | 0 |
| *H. alvei* | 0 | 0 | 1 (100) | 0 |

[a] A patient may have more than one pathogen isolated pre-treatment.

*Reviewer's Comments:*
*The results from this study are supportive of Study AI420-103, but they are not enough to conclude that the applicant's claim against Enterococcus faecalis, Pseudomonas aeruginosa, and Enterobacter spp are true.*

The following table, reproduced from Table 10.1.1C on page 97 of the Study Report, summarizes the response rates based on the complicating factors present on entry.

**Eradication, Persistence, New or Superinfection by Complicating Factors at Test of Cure Visits, Microbiologically Evaluable Patients (Protocol AI420-011)**

| | Number of Patients* (%) | | | | | |
|---|---|---|---|---|---|---|
| | Gatifloxacin N = 81 | | | Ciprofloxacin N = 86 | | |
| | Eradication | Persistence | New/Super infections | Eradication | Persistence | New/Super-infections |
| **Complicating Factor** | **67 (83)** | **4 (5)** | **10 (12)** | **70 (81)** | **4 (5)** | **12 (14)** |
| Indwelling/Intermittent Catheter | 11 (73) | 3 (20) | 1 (7) | 19 (73) | 2 (8) | 5 (19) |
| Ileal Loop | 5 (83) | - | 1 (17) | 5 (71) | 1 (14) | 1 (14) |
| Impaired Bladder Emptying | 26 (81) | 1 (3) | 5 (16) | 26 (96) | - | 1 (4) |
| Obstructive Uropathy | 9 (90) | - | 1 (10) | 4 (67) | 1 (17) | 1 (17) |
| Vesicoureteral Reflux (VUR) or Other Urologic Abnormalities (OUA)[a] | 16 (89) | - | 2 (11) | 16 (80) | - | 4 (20) |

[a] This category does not include ileal loops.
* Pyelonephritis patients are excluded from this table.

*Reviewer's Comments:*
*As with Study AI420-031, the response rates were comparable between the treatment groups.*

8.6.2.1.9. FDA Analyses
The focus of the Division's analyses was the same as in Study AI420-031. The same procedure was utilized. Dr. Silliman utilized the same techniques to assess the strength of the study results.

The tables that from her review that apply to this study are reproduced below, but as before, for complete details, please refer to her review:

**Eradication Rates by Analysis Population**

| Analysis Population | Number Eradicated/Number of Patients (%) Gatifloxacin N = 170 | Ciprofloxacin N = 180 | 95% Confidence Interval* |
|---|---|---|---|
| All Treated Patients | 81/126 (64) | 89/140 (64) | (-11.4%, 13.5%) |
| Clinically Eligible Patients | 80/123 (65) | 88/137 (64) | (-11.6%, 13.2%) |
| Clinically Evaluable Patients | 71/88 (81) | 78/97 (80) | (-12.2%, 12.8%) |
| Microbiologically Evaluable Patients | 71/86 (83) | 78/94 (83) | (-14.5%, 12.4%) |

*For the difference in cure rates, gatifloxacin minus ciprofloxacin.

**Stratified 95% Confidence Intervals by Analysis Population**

| Analysis Population | 95% Confidence Interval for the Difference in Eradication Rates (Gatifloxacin minus Ciprofloxacin) Stratified by Site | Stratified by Diagnosis |
|---|---|---|
| All Treated Patients | (-11.0%, 11.9%) | (-10.6%, 12.7%) |
| Clinically Eligible Patients | — | (-10.6%, 12.8%) |
| Clinically Evaluable Patients | — | (-11.1%, 12.1%) |
| Microbiologically Evaluable Patients | (-11.3%, 13.4%) | (-11.4%, 11.1%) |

Although this study's results were not as strong as they were for Study AI420-03, they are nevertheless supportive of that study and therefore supportive of the applicant's claim of efficacy.

*8.6.2.2 Safety Assessment*

8.6.2.2.1 Extent of Drug Exposure

The following table is an adaptation of Table 9.1 (p. 82) from the applicant's Study Report. It summarized the study drug exposure for Study AI420-011.

**Study Drug Exposure, All Treated Patients (Study AI420-011)**

| | Number of Patients Gatifloxacin N = 170 | Ciprofloxacin N = 180 | Total N = 350 |
|---|---|---|---|
| Number of Days | | | |
| Mean | 9.1 | 9.2 | 9.1 |
| Median | 10 | 10 | 10 |
| Minimum - Maximum | 1 - 13 | 1 – 11 | 1 – 13 |
| Number of Days (%) | | | |
| 1 – 4 | 16 (9) | 13 (7) | 29 (8) |
| 5 – 6 | 9 (5) | 11 (6) | 20 (6) |
| 7 | 2 (1) | 4 (2) | 6 (2) |
| 8 – 9 | 3 (2) | 2 (1) | 5 (1) |

| | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 170 | Ciprofloxacin N = 180 | Total N = 350 |
| 10 | 136 (80) | 142 (79) | 278 (79) |
| >10 | 4 (2) | 8 (4) | 12 (3) |

*Reviewer's Comment*

*As with Study AI420-031 the duration of therapy was comparable between the two treatment groups. The majority of the patients were treated for 10 days.*

8.6.2.2.2 Adverse Events

8.6.2.2.2.1 All Causalities

As with Study AI420-031, the applicant tabulated all adverse events, regardless of causality. Appendix E is a table reproduced from the applicant's Study Report (Table 12.1.1, p. 121), listing the events. The table that follows is a modification of that table, listing the most frequently reported events.

**Most Frequently Reported Adverse Events, All Causality (Study AI420-011)**

| | Number of Patients (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gatifloxacin N = 170 | | | | Ciprofloxacin N = 180 | | | |
| Adverse Clinical Events | Related | Not Related | Not Assessed | Total | Related | Not Related | Not Assessed | Total |
| **Any adverse event** | **74 (44)** | **38 (22)** | **1 (<1)** | **113 (67)** | **54 (30)** | **46 (26)** | **2 (1)** | **102 (57)** |
| Nausea | 27 (16) | 3 (2) | 0 | 30 (18) | 13 (7) | 3 (2) | 0 | 16 (9) |
| Headache | 11 (6) | 5 (3) | 0 | 16 (9) | 8 (4) | 7 (4) | 0 | 15 (8) |
| Dizziness | 8 (5) | 6 (4) | 0 | 14 (8) | 2 (1) | 1 (<1) | 0 | 3 (2) |
| Diarrhea | 11 (6) | 0 | 0 | 11 (6) | 5 (3) | 2 (1) | 0 | 7 (4) |
| Pharyngitis | 1 (<1) | 9 (5) | 1 (<1) | 11 (6) | 0 | 3 (3) | 0 | 3 (3) |
| Pain Abdomen | 5 (3) | 4 (2) | 0 | 9 (5) | 3 (2) | 4 (2) | 0 | 7 (4) |
| Vaginitis (% women) | 8 (10) | 1 (1) | 0 | 9 (11) | 3 (3) | 1 (<1) | 0 | 4 (4) |
| Hematuria | 0 | 8 (5) | 1 (<1) | 9 (5) | 0 | 3 (2) | 0 | 3 (2) |
| Pain Back | 1 (<1) | 5 (3) | 2 (1) | 8 (5) | 3 (2) | 6 (3) | 0 | 9 (5) |
| Vomiting | 7 (4) | 1 (<1) | 0 | 8 (5) | 6 (3) | 2 (1) | 0 | 8 (4) |
| Dysuria | 1 (<1) | 5 (3) | 1 (<1) | 7 (4) | 0 | 4 (2) | 0 | 4 (2) |
| Dry Mouth | 6 (4) | 0 | 0 | 6 (4) | 3 (2) | 2 (1) | 0 | 5 (3) |
| Asthenia | 5 (3) | 1 (<1) | 0 | 6 (4) | 0 | 0 | 1 (<1) | 1 (<1) |

Indication: Complicated Urinary Tract Infections
Study AI420-011

8.6.2.2.2.2 Treatment Related

The following table, an adaptation of Table 12.1.2 from the applicant's Study Report (p. 125) isolates the adverse events that were assessed by the investigator as being study drug-related.

## Drug Related Adverse Clinical Events, All Treated Patients (Study A1420-011)

| | Number of Patients (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gatifloxacin N = 170 | | | | Ciprofloxacin N = 180 | | | |
| Adverse Clinical Event[a] | Mild | Moderate | Severe | Total | Mild | Moderate | Severe | Total |
| **Any drug-related adverse event** | **29 (17)** | **34 (20)** | **10 (6)** | **74 (44)** | **21 (12)** | **25 (14)** | **8 (4)** | **54 (30)** |
| Nausea | 12 (7) | 12 (7) | 3 (2) | 27 (16) | 5 (3) | 6 (3) | 2 (1) | 13 (7) |
| Diarrhea | 6 (4) | 4 (2) | 1 (<1) | 11 (6) | 2 (1) | 2 (1) | 1 (<1) | 5 (3) |
| Headache | 4 (2) | 6 (4) | 1 (<1) | 11 (6) | 3 (2) | 5 (3) | 0 | 8 (4) |
| Dizziness | 4 (2) | 2 (1) | 2 (1) | 8 (5) | 1 (<1) | 1 (<1) | 0 | 2 (1) |
| Vaginitis (% women) | 4 (5) | 3 (4) | 1 (1) | 8 (10) | 3 (3) | 0 | 0 | 3 (3) |
| Vomiting | 1 (<1) | 5 (3) | 1 (<1) | 7 (4) | 1 (<1) | 4 (2) | 1 (<1) | 6 (3) |
| Dry Mouth | 2 (1) | 4 (2) | 0 | 6 (4) | 2 (1) | 1 (<1) | 0 | 3 (2) |
| Pain Abdomen | 3 (2) | 1 (<1) | 1 (<1) | 5 (3) | 0 | 2 (1) | 1 (<1) | 3 (2) |
| Insomnia | 3 (2) | 2 (1) | 0 | 5 (3) | 0 | 1 (<1) | 0 | 1 (<1) |
| Asthenia | 2 (1) | 2 (1) | 1 (<1) | 5 (3) | 0 | 0 | 0 | 0 |
| Somnolence | 2 (1) | 2 (1) | 0 | 4 (2) | 0 | 0 | 1 (<1) | 1 (<1) |
| Dyspepsia | 0 | 3 (2) | 0 | 3 (2) | 2 (1) | 2 (1) | 1 (<1) | 5 (3) |
| Constipation | 1 (<1) | 1 (<1) | 0 | 2 (1) | 1 (<1) | 3 (2) | 0 | 4 (2) |
| Nervousness | 1 (<1) | 0 | 1 (<1) | 2 (1) | 0 | 1 (<1) | 1 (<1) | 2 (1) |
| Spasm | 1 (<1) | 1 (<1) | 0 | 2 (1) | 0 | 0 | 0 | 0 |
| Taste perversion | 2 (1) | 0 | 0 | 2 (1) | 0 | 0 | 0 | 0 |
| Oral Moniliasis | 1 (<1) | 0 | 0 | 1 (<1) | 2 (1) | 0 | 0 | 2 (1) |
| Sweating | 0 | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 2 (1) |
| Pain Back | 1 (<1) | 0 | 0 | 1 (<1) | 2 (1) | 0 | 1 (<1) | 3 (2) |
| Rash | 0 | 0 | 0 | 0 | 0 | 4 (2) | 0 | 4 (2) |

[a] Only those adverse events occurring in 1% or more of the patients in either treatment group are listed here. For full listing see Appendix 16B.

*Reviewer' Comments*

*The findings were similar as before, in that there were more adverse events assessed as being study drug-related in the gatifloxacin treatment group than in the ciprofloxacin treatment group, predominantly driven by nausea. However, more were categorized as "moderate – Grade II" in this study.*

*Another difference between the two studies is that diarrhea, headache, and vaginitis were more prominent complaints in this study.*

8.6.2.2.2.3 Serious Adverse Events

The applicant reported that a total of 10 patients experienced serious adverse events. There were 7 in the gatifloxacin treatment group and 3 in the ciprofloxacin treatment group. Of the 7 patients in the gatifloxacin arm, none were assessed by the investigator as having experienced events with causality assigned to the study drug. In the ciprofloxacin arm, there was one.

The table on the next page is an adaptation of Table 12.3 (p. 128) in the applicant's Study Report, and summarizes the types of serious adverse events that were reported, as well as their investigator-assessed relationship.

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## Serious Adverse Clinical Events of All Causes, All Treated Patients (Study AI420-011)

| | Number of Patients (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gatifloxacin N = 170 | | | | Ciprofloxacin N = 180 | | | |
| Adverse Clinical Event | Related | Not Assessed | Not Related | Total | Related | Not Assessed | Not Related | Total |
| Any serious event | - | - | 7 (4) | 7 (4) | 1 (<1) | - | 2 (1) | 3 (2) |
| Congestive heart failure | - | - | 1 (<1) | 1 (<1) | - | - | - | - |
| Nausea | - | - | - | - | 1 (<1) | - | - | 1 (<1) |
| Vomiting | - | - | - | - | 1 (<1) | - | - | 1 (<1) |
| Skin Ulcer | - | - | 1 (<1) | 1 (<1) | - | - | - | - |
| Cerebrovascular Accident | - | - | 1 (<1) | 1 (<1) | - | - | - | - |
| Headache | - | - | - | - | - | - | 1 (<1) | 1 (<1) |
| Hydrocephalus | - | - | - | - | - | 1 (<1)[a] | - | 1 (<1)[a] |
| Infection Urinary Tract | - | - | - | - | - | - | 1 (<1) | 1 (<1) |
| Dementia | - | - | 1 (<1) | 1 (<1) | - | - | - | - |
| Convulsion | - | - | 1 (<1) | 1 (<1) | - | - | - | - |
| Carcinoma Bladder | - | - | 1 (<1) | 1 (<1) | - | - | - | - |
| Disorder Prostate | - | - | 1 (<1) | 1 (<1) | - | - | - | - |
| Urolithiasis | - | - | 1 (<1) | 1 (<1) | - | - | - | - |

[a] The relationship to study treatment was not recorded.

*Reviewer's Comments*

*The applicant reported that no patient on the gatifloxacin treatment group experienced a serious adverse event that was assessed as being "related" to the study drug.*

*There was one patient on the gatifloxacin treatment group who had a seizure, felt to be unrelated to study drug therapy:*

*Patient #007-0086 was a 26 year-old whitte female, enrolled with a diagnoisis of complicated urinary tract infection. She had a past medical history that included Crohn's disease, fibromyalgia, and seizures disorder. Her chronic medications included clonazepam, divalproex, lamotrigine, mercaptopurine, [redacted] and metaxalone. She was treated from 9/5/97 to 9/14/97, and although she had some complaints of nausea and vomiting, this was felt to not be increased from her baseline, and presumed to be due to her chronic medications. She experienced a seizure on 10/3/97 and was subsequently admitted to her local hospital; the course of the hospitalization is not apparent from the case report form, however the assessment of the investigator was that the seizure episode was unlikely to be due to study drug therapy. Review of the case report form did not reveal any information to warrant changing the investigator's assessment. The temporal relationship, plus the patients past medical history of seizures, makes it difficult to attribute this episode to gatifloxacin therapy.*

*Review of the SAS transport data files identified a ciprofloxacin patient that apparently experienced a serious adverse event, which was not reported in the applicant's summary table. Patient #007-0087 was a 50 year-old white female enrolled with a diagnosis of complicated UTI, who had a left knee replacement a month after terminating therapy. The investigator assessed the severity as Grade III, and felt that it was unrelated to study drug. Review of the case report form did not reveal any information to contradict the investigator's assessment. Although it would have been preferable that this patient's adverse event would have been included in the summary table, it is believed that its omission is not critical.*

8 6.2.2.2.4 Severe and Life-threatening Events

There were no severe and life-threatening adverse events reported for this study.

8 6.2.2.2.5 Discontinuation from Studies

8 6.2.2.2.5.1 Discontinuations Due to Adverse Events

The following table summarizes the number of patients that were discontinued due to adverse events, and the types of adverse events that were observed. It is adapted from Table 12.4 (p.130) in the applicant's Study Report.

**Discontinuation of Study Medication Due to Adverse Clinical Events, All Treated Patients (Study AI420-011)**

| | Number of Patients | | |
|---|---|---|---|
| | Gatifloxacin N = 170 | Ciprofloxacin N = 180 | Total N = 350 |
| Number Discontinued[a] | 17 | 16 | 33 |
| Adverse Event[b] | | | |
| Nausea | 10 (9)[c] | 5 (4) | 15 (13) |
| Vomiting | 7 (6) | 2 (2) | 9 (8) |
| Headache | 2 (2) | 2 (1) | 4 (3) |
| Rash | 0 | 4 (4) | 4 (4) |
| Pain back | 1 (0) | 2 (1) | 3 (1) |
| Dyspepsia | 2 (2) | 1 (1) | 3 (3) |
| Pain abdomen | 1 (1) | 1 (0) | 2 (1) |
| Diarrhea | 1 (1) | 1 (1) | 2 (2) |
| Insomnia | 2 (2) | 1 (1) | 3 (3) |
| Nervousness | 1 (1) | 1 (1) | 2 (2) |
| Somnolence | 1 (1) | 1 (1) | 2 (2) |
| Edema (peripheral) | 0 | 2 (1) | 2 (1) |

a Only events that occurred in 2 or more patients are included in this table.
b Patients may be included in one or more adverse clinical event.
c ( ) = drug related adverse event.

*Reviewer's Comments*
*Except for the categories of nausea and vomiting, the numbers of patients that discontinued due to adverse events were comparable between the two treatment groups.*

8.6.2.2.2.5.2 Discontinuations Due to Laboratory Abnormalities

As in Study AI420-031, the protocol contained guidelines to help determine when a patient should have study drug dose adjustments. Please refer to Section 8.6.1.2.2.5.2 of this review to see the toxicity grades guidelines that were used.

*Reviewer's Comments*
*Three patients (2 gatifloxacin and 1 ciprofloxacin ) were discontinued from study drug because of an elevated baseline serum creatinine.*

*Of the patients that had deviations from normal pre-treatment values, most were mild in severity. There were 3 patients (2 gatifloxacin and 1 ciprofloxacin patient) who manifested Grade 3 or greater abnormality. With respect to the gatifloxacin patients:*

*Patient #007-0194 was a 66 year-old female who experienced an elevated serum amylase to 220 U/L on Day +8 from a baseline value of 46 U/L. Level was normal by Day +33.*

*Patient #004-0354 was a72 year-old white male who had a serum chloride of 79 mEq/L on Day +8 (from a baseline of 103 mEq/L). The patient had an intravenous pyelogram on the same day. Serum chloride levels had normalized by Day +45.*

*Of the patients that had abnormal pre-treatment values, 6 patients experienced deviations of at least Grade III (3 patients in each treatment group); none of the gatifloxacin patients required discontinuation of their study drug.*

8.6.2.2.2.6 Assessment of Drug Relationship for Selected Adverse Events

As with Study AI420-031, the SAS transport data files were reviewed for hepatic enzyme and serum amylase abnormalities.

8.6.2.2.2.6.1 Hepatobiliary System Abnormalities

Fifteen patients had elevated total bilirubin values while on therapy (11 gatifloxacin and 4 ciprofloxacin). Of the 11 gatifloxacin patients, 6 had normal pre-treatment values. Of these 6 patients, 5 had isolated elevations in the serum total bilirubin. The patient that also had elevated transaminases also had elevated transaminases at baseline (Patient #012-0103).

8.6.2.2.2.6.2 Pancreatic Enzyme Abnormalities

Sixteen patients had elevated serum amylase while on therapy (9 gatifloxacin and 7 ciprofloxacin). Of the 9 gatifloxacin patients, 4 had normal pre-treatment values. The average increase in this group was 91 U/L [redacted] none of the patients complained of abdominal pain. As in Study AI420-031, of the 4 patients, 3 were females, elderly (> 66 years of age), 2 had elevated serum creatinine.

As in Study AI420-031, of the patients that had an abnormal serum amylase at baseline, the majority improved while on therapy.

The conclusions are the same as for Study AI 420-031: asymptomatic elevation in serum amylase occurred, predominantly in elderly females and perhaps reflective of mild renal insufficiency.

8.6.2.2.2.7 Mortality Experience

There was a death in each of the treatment group; neither was attributed to the study drug by the investigator. Gatifloxacin patient # 004-0257 died on Day +3 from a cerebrovascular accident, and ciprofloxacin patient # 004-0263 died on Day +50 from recurrent bladder cancer.

*Reviewer's Comments*

*Review of the case report form did not reveal any information to reject the investigator's assessment.*



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## 8.6.3 FDA Summary

### *8.6.3.1 Efficacy Summary for this Indication*

The two clinical trials in support of proposed indication, Protocols AI420-011, and AI420-031 had the following number of patients:

| | | Number of Subjects | | | |
|---|---|---|---|---|---|
| Study No. | Study Dates | Randomized | Treated | Clinically Eligible | Microbiologically Eligible |
| AI420-011 | 7/27/97 – 6/3/98 | 354 | 350 | 340 | 180 |
| AI420-031 | 8/20/97 – 7/11/98 | 376 | 372 | 356 | 186 |
| | Total | 730 | 722 | 696 | 366 |

This reviewer's conclusion is that the applicant has provided sufficient data to demonstrate that their claim that gatifloxacin is as effective as ciprofloxacin for this indication is true. It is not believed that the applicant has demonstrated efficacy for all the pathogens that they claim in their label. This will need to be addressed in the final approved labeling of the product.

### *8.6.3.2 Safety Summary for this Indication*

The principal safety database for this indication consists of the patients that participated in studies AI402-011 and AI420-031. This database is supplemented by the safety data that was generated by the other clinical trials that were conducted in support of this application. Dr. Joyce Korvick, the Division's lead medical reviewer for this application, performed the integrated safety assessment. Please refer to Section 9.0 of the clinical review for complete details.

8.6.3.2.1 Extent of Drug Exposure in this Indication

The following table, adapted from the Integrated Summary of Safety and Efficacy (p. 337), summarizes the pooled duration of exposure for the two clinical studies:

| | Number (%) of patients | |
|---|---|---|
| | Gatifloxacin (N = 359) | Ciprofloxacin (N = 363) |
| Mean | 9 | 9 |
| Median | 10 | 10 |
| Min – Max | 1 – 13 | 1 – 12 |
| Duration (days) | | |
| < 7 | 48 (13) | 44 (12) |
| 7 | 11 ( 3) | 16 ( 4) |
| 8 – 9 | 11 ( 3) | 9 ( 2) |
| 10 | 282 (79) | 283 (78) |
| >10 | 7 ( 2) | 11 ( 3) |

This provided a safety database of 359 for this indication. As mentioned above, this safety database was also interpreted in the context of the entire safety database submitted by the applicant for the complete New Drug Application (NDA).

8.6.3.2.2 Summary of Adverse Events

8.6.3.2.2.1 All Causalities

The following table, which is a combination of the two tables presented for each of the studies, summarizes the safety data for this indication:

All-Cause Adverse Events

| Adverse Clinical Event* | Gatifloxacin | | | | | | Ciprofloxacin | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 011 N = 170 | | 031 N = 189 | | Total N = 359 | | 011 N = 180 | | 031 N = 183 | | Total N = 363 | |
| | N | % | N | % | N | % | n | % | n | % | n | % |
| Any AE | 113 | 66.5 | 97 | 51.3 | 210 | 58.5 | 102 | 56.7 | 79 | 43.2 | 181 | 49.9 |
| Nausea | 30 | 17.6 | 24 | 12.7 | 54 | 15 | 16 | 8.9 | 11 | 6 | 27 | 7.4 |
| Dizziness | 14 | 8.2 | 14 | 7.4 | 28 | 7.8 | 3 | 1.7 | 5 | 2.7 | 8 | 2.2 |
| Headache | 16 | 9.4 | 6 | 3.2 | 22 | 6.1 | 15 | 8.3 | 10 | 5.5 | 25 | 6.9 |
| Diarrhea | 11 | 6.5 | 7 | 3.7 | 18 | 5 | 7 | 3.9 | 9 | 4.9 | 16 | 4.4 |
| Pharyngitis | 11 | 6.5 | 5 | 2.6 | 16 | 4.5 | 3 | 1.7 | 5 | 2.7 | 8 | 2.2 |
| Pain Abdomen | 9 | 5.3 | 5 | 2.6 | 14 | 3.9 | 7 | 3.9 | 10 | 5.5 | 17 | 4.7 |
| Pain Back | 8 | 4.7 | 6 | 3.2 | 14 | 3.9 | 9 | 5 | 4 | 2.2 | 13 | 3.6 |
| Vomiting | 8 | 4.7 | 6 | 3.2 | 14 | 3.9 | 8 | 4.4 | 5 | 2.7 | 13 | 3.6 |
| Hematuria | 9 | 5.3 | 4 | 2.1 | 13 | 3.6 | 3 | 1.7 | 5 | 2.7 | 8 | 2.2 |
| Vaginitis | 9 | 5.3 | 3 | 1.6 | 12 | 3.3 | 4 | 2.2 | 3 | 1.6 | 7 | 1.9 |
| Dysuria | 7 | 4.1 | 5 | 2.6 | 12 | 3.3 | 4 | 2.2 | 12 | 6.6 | 16 | 4.4 |
| Dry mouth | 6 | 3.5 | 5 | 2.6 | 11 | 3.1 | 5 | 2.8 | 0 | 0 | 5 | 1.4 |
| Pain | 3 | 1.8 | 8 | 4.2 | 11 | 3.1 | 5 | 2.8 | 1 | 0.5 | 6 | 1.7 |
| Urinary retention | 3 | 1.8 | 5 | 2.6 | 8 | 2.2 | 4 | 2.2 | 4 | 2.2 | 8 | 2.2 |

*A patient may have more than one adverse event